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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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EXAMINER

KAM, CHIH MIN

| ART UNIT | PAPER NUMBER |
|----------|--------------|
| 1653 | |

DATE MAILED: 12/11/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------------|-----------------|--------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 09/741,106 | INNIS ET AL. |
| | Examiner | Art Unit |
| | Chih-Min Kam | 1653 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 11 October 2002.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-87 is/are pending in the application.
- 4a) Of the above claim(s) 28-72 and 74-87 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-27 and 73 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) Notice of References Cited (PTO-892) 4) Interview Summary (PTO-413) Paper No(s). _____.
2) Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) Notice of Informal Patent Application (PTO-152)
3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5. 6) Other: _____

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-27 and 73; protease nexin-2 as the heparin binding domain in claims 8 and 22, SEQ ID NO:10 in claims 9 and 23; and SEQ ID NO:12 as the second amino acid sequence in claim 15 in Paper No. 10 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Upon reconsideration, all proteins ((a)-(h)) in claims 8 and 22, all sequences ((a)-(i)) in claims 9 and 23; and all sequences ((a)-(k)) in claim 15 will be examined. Thus, claims 1-27 and 73 are examined. The requirement is still deemed proper and is therefore made FINAL.

Informalities

The disclosure is objected to because of the following informalities:

2. The specification is objected to because of the use of [...] in the text, e.g., “[SEQ ID NO:1]” at page 6, lines 9, 14, 19, 24 and 29. Bracketing or underlining are commonly used to indicate amendments or changes in the claims as provided in 37 CFR 1.121(a)(2)(ii) and are normally not intended to be printed in the published patent. Please note current requirements for amendments which require a clean copy of the amendatory material and a marked copy.

Claim Objections

3. Claims 10, 11, 16-18, 24 and 25 are objected to because of the use of [...] in the claim. Bracketing or underlining are commonly used to indicate amendments or changes in the claims as provided in 37 CFR 1.121(a)(2)(ii) and are normally not intended to be printed in the published patent. For example, in claim 10, applicant has used “[SEQ ID NO:7]” in such a

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manner that appears that the instant brackets would indicate deleted material and is thus, confusing as to whether the amino acid sequence in claim 10 would include "SEQ ID NO:7" or not. The applicant can only amend by cancellation and presentation of a new claim. See also changes to 37 CFR 1.121 in Amendment rules package (Final Rule published on 8 Sep. 2000 (65 Fed. Reg. 54603), see also O. G. of 19 Sep. 2000 (1238 Off. Gaz. Pat. Office 77)).

Claim Rejections-Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1-12, 16-25 and 73 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U. S. Patent 6,174,721.

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-12, 16-25 and 73 in the instant application disclose a chimeric protein comprising a Kunitz-type domain 1 of TFPI or a mutein thereof, and a Kunitz-type domain 2 of TFPI-2 or a mutein thereof; or a Kunitz-type domain 1 of TFPI-2 or a mutein thereof, and a Kunitz-type domain 2 of TFPI or a mutein thereof. This is obvious in view of claims 1-17 in the patent which disclose a chimeric protein comprising a Kunitz-type domain 1

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of TFPI and a Kunitz-type domain 2 of TFPI-2; or a Kunitz-type domain 1 of TFPI-2 and a Kunitz-type domain 2 of TFPI, wherein chimeric protein lacks sites for N-glycosylation. Both sets of claims cite a chimeric protein comprising a Kunitz-type domain 1 of TFPI and a Kunitz-type domain 2 of TFPI-2; or a Kunitz-type domain 1 of TFPI-2 and a Kunitz-type domain 2 of TFPI. Thus, claims 1-12, 16-25 and 73 in present application and claims 1-17 in the patent are obvious variations of a chimeric protein comprising a Kunitz-type domain 1 of TFPI and a Kunitz-type domain 2 of TFPI-2; or a Kunitz-type domain 1 of TFPI-2 and a Kunitz-type domain 2 of TFPI.

5. Claims 1-12, 16-27 and 73 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of U. S. Patent 5,589,359.

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-12, 16-27 and 73 in the instant application disclose a chimeric protein comprising a Kunitz-type domain 1 of TFPI or a mutein thereof, and a Kunitz-type domain 2 of TFPI-2 or a mutein thereof; or a Kunitz-type domain 1 of TFPI-2 or a mutein thereof, and a Kunitz-type domain 2 of TFPI or a mutein thereof. This is obvious in view of claims 1-24 in the patent which disclose a chimeric protein comprising a Kunitz-type domain 1 of TFPI and a Kunitz-type domain 2 of TFPI-2; or a Kunitz-type domain 1 of TFPI-2 and a Kunitz-type domain 2 of TFPI. Both sets of claims cite a chimeric protein comprising a Kunitz-type domain 1 of TFPI and a Kunitz-type domain 2 of TFPI-2; or a Kunitz-type domain 1 of TFPI-2 and a Kunitz-type domain 2 of TFPI. Thus, claims 1-12, 16-27 and 73 in present application and claims 1-24 in the patent are obvious variations of a chimeric protein comprising

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a Kunitz-type domain 1 of TFPI and a Kunitz-type domain 2 of TFPI-2; or a Kunitz-type domain 1 of TFPI-2 and a Kunitz-type domain 2 of TFPI.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 2-13 and 16-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a chimeric protein comprising a Kunitz-type domain 1 of TFPI and a Kunitz-type domain 2 of TFPI-2; or a Kunitz-type domain 1 of TFPI-2 and a Kunitz-type domain 2 of TFPI; or, a chimeric protein comprising certain muteins of TFPI or TFPI-2 which has an identified mutation in the Kunitz-type domain such as the substitution at P1 reactive site of Kunitz-type domain, does not reasonably provide enablement for a chimeric protein containing any mutein of Kunitz domain 1 or 2 of TFPI or TFPI-2, where the mutation is not identified, or a chimeric protein having a generic structure, A-(X₁)_a-B-(X₂)_b-C, wherein a=0, b=0 or a=b=0, or, A=B=C=0 and a=b=0. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 2-13 and 16-25 encompass a chimeric protein comprising a Kunitz-type domain 1 of TFPI or a mutein thereof, and a Kunitz-type domain 2 of TFPI-2 or a mutein thereof; or a Kunitz-type domain 1 of TFPI-2 or a mutein thereof, and a Kunitz-type domain 2 of TFPI or a mutein thereof. However, the specification only indicates the mutein of TFPI or TFPI-2 has 1-5 amino acid substitutions in the wild-type sequence, it does not identify most substitutions in the

TFPI or TFPI-2 (page 7, line 26-page 8, line 3; page 8, line 19-page 9, line 21). There are no indicia that the present application enables the full scope in view of the muteins of TFPI or TFPI-2 as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the claims are enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the scope of the claims, the state of the prior art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the muteins of TFPI or TFPI-2, which are not adequately described or demonstrated in the specification.

(2). The presence of working examples:

The specification has shown the mutein has the amino acid sequence of SEQ ID NO:9 (276 amino acid residues) or SEQ ID NO:19 (161 amino acid residues), where a Lys at position 36 is substituted with Arg. There are no other working examples indicating the claimed variants.

(3). The state of the prior art and relative skill of those in the art:

The prior art (WO 91/02753) indicates TFPI with certain amino acid residues such as C-terminal region deleted has TFPI activity but with no or low heparin binding activity, however, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the identities of the muteins and the effects of the chimeric proteins containing the muteins to be considered enabling for variants.

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(4). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claimed invention is directed to a chimeric protein comprising a Kunitz-type domain 1 of TFPI or a mutein thereof, and a Kunitz-type domain 2 of TFPI-2 or a mutein thereof; or a Kunitz-type domain 1 of TFPI-2 or a mutein thereof, and a Kunitz-type domain 2 of TFPI or a mutein thereof. The specification only indicates muteins have 1-5 amino acid substitutions in the wild-type sequence, it does not specify where the substitutions are except for the substitution at the P1 reactive site and substitutions at positions within 5 amino acids of the P1 reactive sites in Kunitz-type domains (page 7, line 26-page 8, line 3; page 8, line 19-page 9, line 21). Moreover, there are no working examples indicating various muteins except for substitution at P1 reactive site of Kunitz-type domains, e.g., SEQ ID NO:9. The specification also indicates a chimeric protein can have a generic structure, A-(X₁)_a-B-(X₂)_b-C, wherein A or C contains 0-100 amino acids, B contains 1-25 amino acids, and a and b are integers from 0-6 (page 10, line 13-page 11, line 5), however, when A=C=0, B=1 and a=b=0, the structure is an amino acid, not a chimeric protein; or when a=0, b=0 or a=b=0, the structure does not have a chimeric protein.

Since the specification fails to provide sufficient guidance on identities of various muteins or the effects of the chimeric proteins containing the muteins, it is necessary to have additional guidance on the muteins and to carry out further experimentation to make/use chimeric proteins containing the muteins, and assess the inhibitory effects to Factor VIIa/TF/Xa.

(5). Predictability or unpredictability of the art:

As indicated in the previous sections, the specification only demonstrates the substitution at the P1 reactive site such as in SEQ ID NO:9 or 19, it does not identify various substitutions in

muteins of TFPI and TFPI-2. Since the claims encompass numerous unidentified variants, the effects of the chimeric proteins containing various muteins of TFPI and TFPI-2 are unpredictable.

(6). Nature of the Invention

The scope of the claims includes many structural variants, however the specification has not identified these variants nor indicated the effects of the chimeric proteins containing these variants. Thus, the disclosure is not enabling for reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants, and the guidance and the teaching in the specification is limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the inhibitory effect of the claimed invention toward Factor VII/TF/Xa.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 2-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 2-13 are indefinite because of the use of the term "wherein a,b are integers from 0-6" or "wherein A,B,C,D,E,F,G may comprise portions of native TFPI or TFPI-2 sequences or non-native sequence". The term "wherein a,b are integers from 0-6" or "wherein A,B,C,D,E,F,G may comprise portions of native TFPI or TFPI-2 sequences or non-native sequence" renders the

claim indefinite, it is unclear how a compound in generic formula A-(X₁)_a-B-(X₂)_b-C having a=0, b=0 or a=b=0 can be a chimeric protein? When A=B=C=0 and a=b=0 in the formula, the length is zero. It is also unclear whether A, B, C, D, E, F or G comprises portions of native TFPI or TFPI-2 sequences or non-native sequence as to "may comprise", and which portions of native TFPI or TFPI-2 sequences or non-native sequence are intended. Claims 2-13 are also indefinite because claim 2 cites a mutein of Kunitz-type domain 1 or 2 of TFPI or TFPI-2, which does not further limit claim 1. Claims 3-13 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend.

9. Claims 14 and 15 are indefinite because claim 14 cites SEQ ID NO:19 which does not contain a Kunitz-type domain 1 of TPFI-2, it contains a mutated Kunitz-type domain 1 of TPFI and a Kunitz-type domain 2 of TPFI. Claim 15 is included in the rejection because it is dependent on a rejected claim and does not correct the deficiency of the claim from which it depends.

10. Claims 16-25 are indefinite because claim 16 cites a mutein of Kunitz-type domain 1 or 2 of TFPI or TFPI-2, which does not further limit claim 1. Claims 17-25 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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11. Claim 2 is rejected under 35 U.S.C. 102(b) as anticipated by Voet *et al.* (Biochemistry (text book), page 59-63 (1990)).

Voet *et al.* teach an amino acid having different side chain (Table 4-1) which meets the criteria of claim 2, when the generic structure A-(X₁)_a-B-(X₂)_b-C in the claim has a=b=0, B=1, and A=C=0.

Conclusion

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8:00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. *CMK*
Patent Examiner

December 9, 2002

Christopher S. F. Low

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